IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

James Norman CAWSE Group Art Unit: 1631

Application No.: 09/681,753 Examiner: Lori A. Clow

Filed: May 31, 2001

For: METHOD AND SYSTEM TO CONDUCT A COMBINATORIAL HIGH THROUGHPUT SCREENING EXPERIMENT

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D. C. 20231

Sir:

I, James N. Cawse, a citizen of the United States of America, do hereby declare and state:

1. This Declaration is submitted as evidence that I am the inventor of the subject matter disclosed in Cawse et al. "Combinatorial Search and Experimental Design Techniques" slide presentation (hard copy attached) that was relied upon to reject claim 12 in the June 17, 2003 Office Action in the above-identified Application.

2. In the Office Action, claim 12 was rejected under 35 U.S.C. §103(a) over Argrafotis et al. (U.S. Pat. 5,901,069 and Cawse et al. "Combinatorial Search and Experimental Design Techniques" slide presentation.

3. The Office Action states that:

> Agrafiotis teaches a computer-based, iterative process for generating chemical entities with defined physical chemical and/or bioactive properties (see abstract). Agrafiotis et al. do not teach a specific model to define an experimental space, however, Cawse et al. do teach the Latin Square model for combinatorial design on page 12 of the Combinatorial Search and Design Techniques slide presentation. It would have been prima facie obvious to use the Latin Square Modeling method in the generation of a synthesis model in Agrafiotis et al. to improve design runs.

Office Action pages 5 to 6.

4. James N. Cawse is one of the authors of the Cawse et al. "Combinatorial Search and Experimental Design Techniques" slide presentation (hard copy attached) and is the sole inventor of the invention of the present Application as claimed in claims 1 to 34.

5. James N. Cawse is the author of the subject matter from Cawse et al. "Combinatorial Search and Experimental Design Techniques" that was relied upon in the Office Action to reject claim 12 under 35 U.S.C. §103(a) over Argrafotis et al. (U.S. Pat. 5,901,069 and the Cawse et al. "Combinatorial Search and Experimental Design Techniques" slide presentation.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

James N Cawse

James N. Cawse

Schenectady, New York
7/8, 2003

Combinatorial Search and Experimental Design Techniques

James N. Cawse
Necip Doganaksoy
Robert Mattheyses
Tom Repoff
William Tucker
Yu-To Chen
Carl Hansen
Chandrasekha Pisupati
Christopher Stanard

The 1999 ASA Quality and Productivity Research Conference
May 19-21, Schenectady, New York

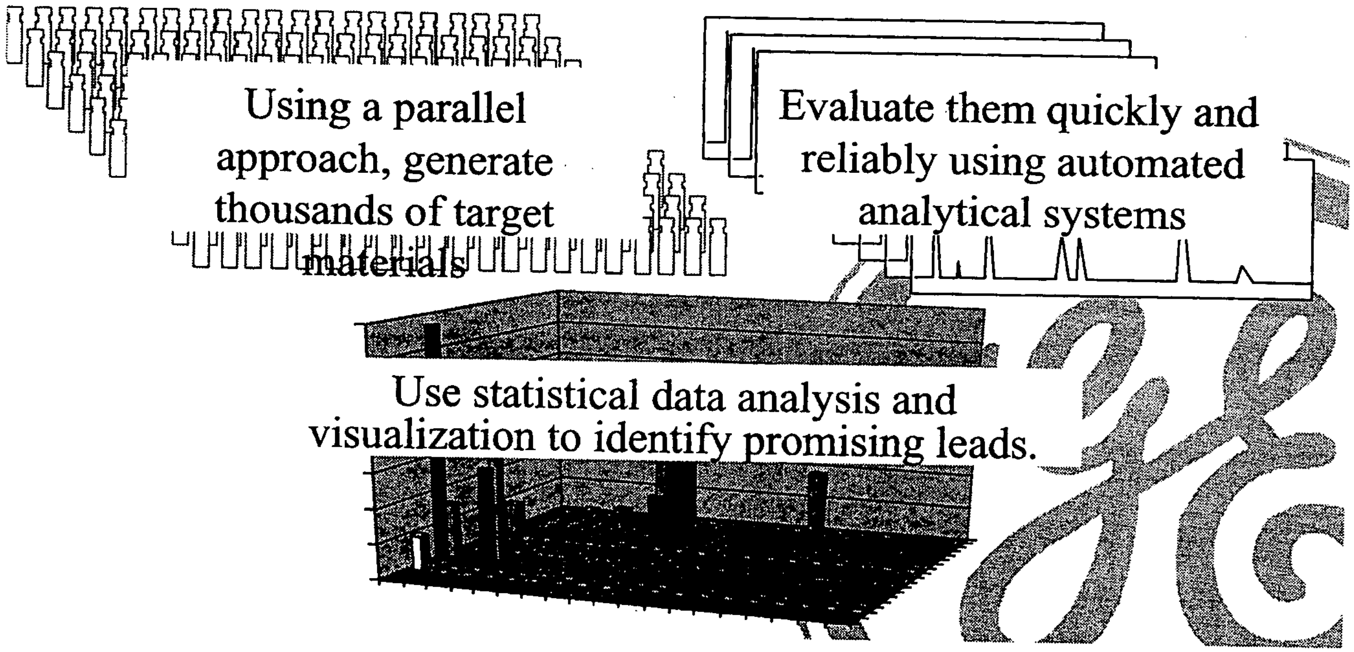
Outline

- Background
  - Why combinatorial Chemistry?
  - Difference between Drug and Materials CombiChem
- Data Management and Quality
- Experimental Design
- Data Analysis and Visualization

Combinatorial Materials Development

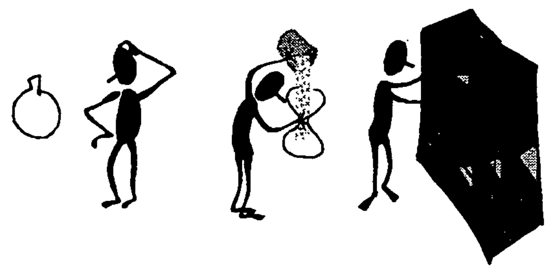
What is it?

An experimental approach to rapidly identify or optimize new material compositions.



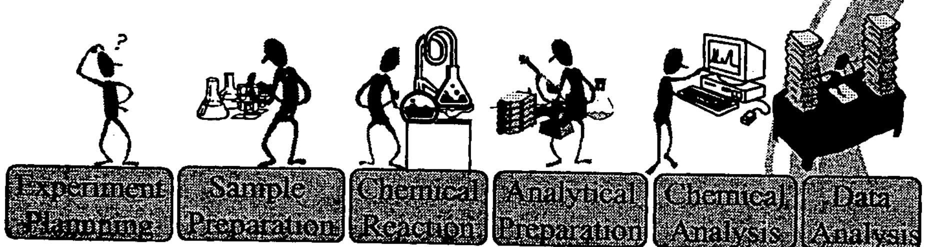
Why Combinatorial Technology?

1890's - 1990's: Chemist as an individual artisan



1-1000 g/experiment
1-2 Experiments/day
100-500 Expts/year
1-2 new leads/year

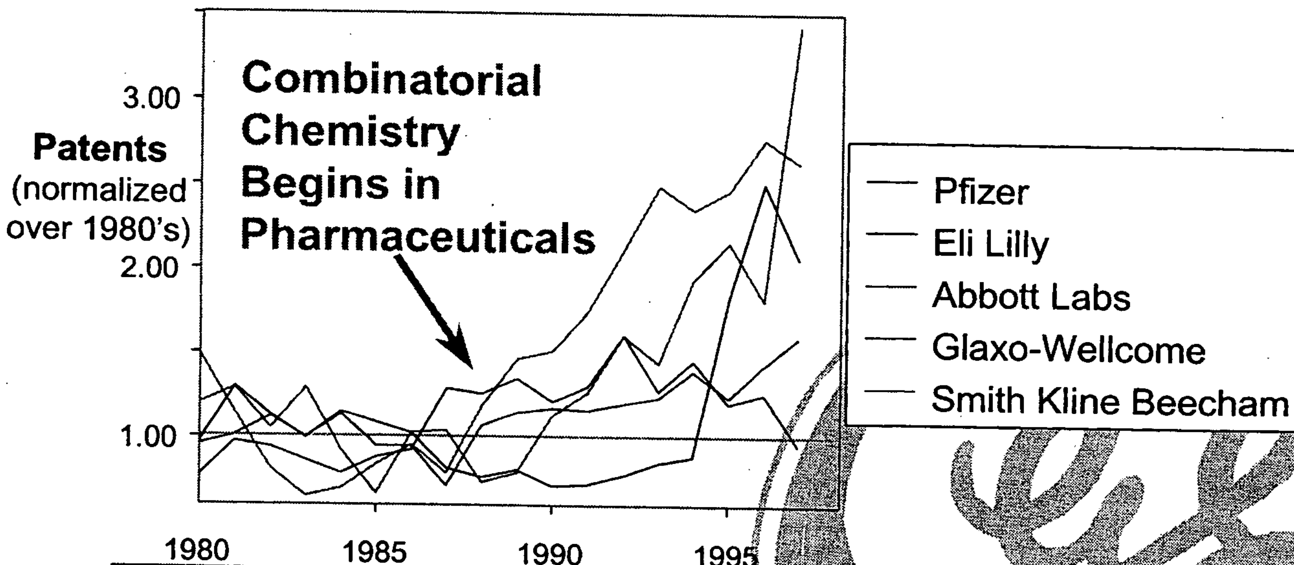
1990's - 21st Century: Combinatorial Development Team



1-100 mg/experiment
10-200 Experiments/day
1000-10,000 Expts/year
>10 new leads/year

High Speed Innovation

Combinatorial Approach Accelerates the Generation of Patentable Inventions.



Increase in Patents from Pharmaceutical Companies corresponds to their use of Combinatorial Chemistry.

Potential Applications Outside the Pharmaceutical Industries

- Plastics
  - Catalysts, Carbon Fibrils, Blends,...
- Lighting
  - Fluorescent lamp cathodes, Phosphors, LEDs,...
- Medical Systems
  - Scintillators, superconductors, ...
- Aircraft Engines and Turbines
  - Coatings, alloys…

Difference Between Pharmaceutical and Materials Development Combinatorial Design

- **Pharmaceutical**
  - Focused on chemical synthesis only
  - Emphasis on diversity within known metrics
  - Experimental space metrics known
  - Easy sample evaluation on nanogram level
  - Challenge is deconvolution of mixtures of very large numbers ($>10^6$) of molecules
- **Materials Development**
  - Synthesis, mixtures, and process variables
  - Emphasis on broad coverage and synergy
  - Experimental space metrics not known
  - Sample evaluation difficult and individual for each system
  - Challenge is finding high order synergies of qualitative and mixture/process variables

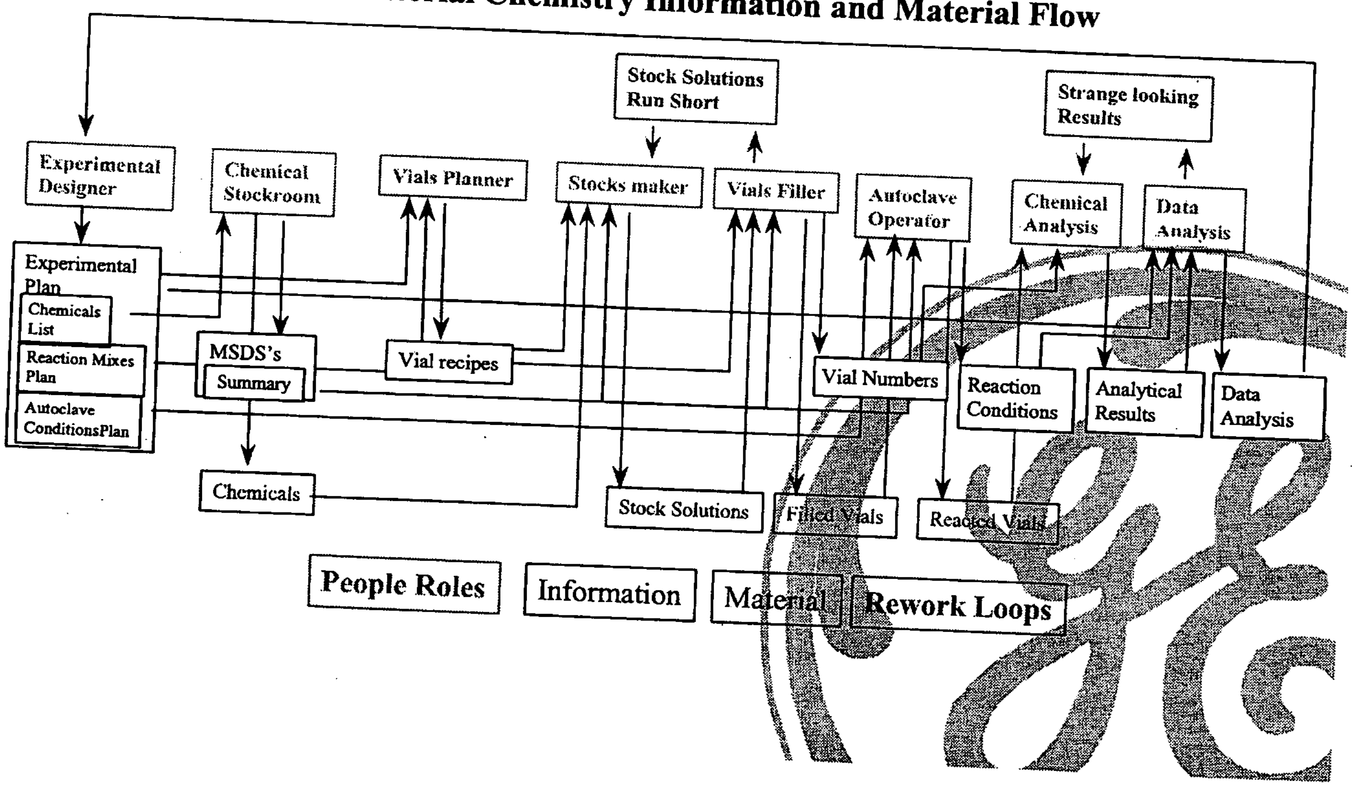
General concepts carry over but new thinking is needed

Data Management and Quality Issues

- Complex, interrelated system
  - Design for Six Sigma discipline required
- Massive number of individual data elements
  - Database needed to contain and control data flow
  - Barcoding system required to minimize errors
- Multiple sources of defects
  - Six Sigma quality required to get good data
  - Quality specification in terms of system variance

Data Management

Combinatorial Chemistry Information and Material Flow



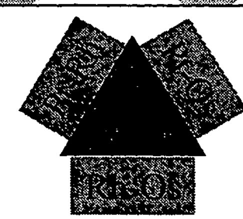
Experimental Design:
What are the Dimensions of the Problem?

Formulation Factors	Type	Levels
Primary Catalyst	Qualitative	1
Inorganic Cocatalyst	Qualitative	20
Amount of Cocatalyst	Quantitative	3
Organic Ligand	Qualitative	20
Amount of Ligand	Quantitative	3
Active Anion	Qualitative	10
Amount of Anion	Quantitative	3
Process Factors		
Reaction Time	Quantitative	3
Reaction Temperature	Quantitative	3
Reaction Pressure	Quantitative	3
Total Number of Potential Runs:		**2,916,000**

Even at 100 - 1000 runs/day, a highly fractionated design needed!

Why Won't Traditional DOE Strategies Work?

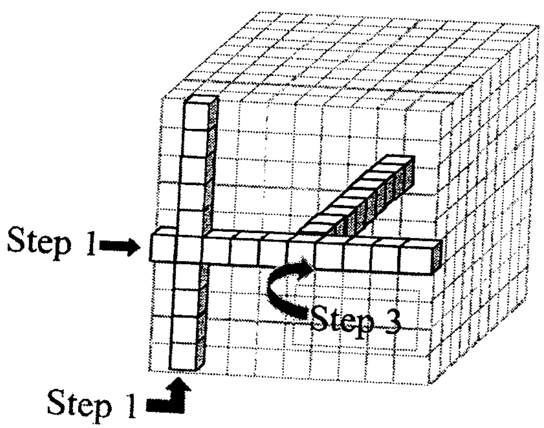
- RSM approaches won't work with qualitative factors
- High/Low designs don't give needed resolution
- Formulation/Process variables lead to nested situations
- Need very high fractionation of design space
- Main effects unimportant or trivial
- High order synergies are the goal:



A highly active ternary catalyst bounded by low activity binaries
T.E. Mallouk *et. al.*, *Science*, **1998**, 1735

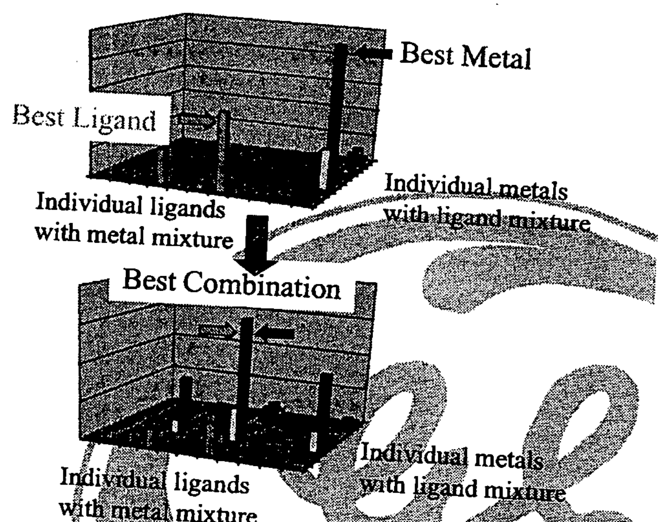
Early Attempts at Strategies

"Representational" Strategy



8000 possibilities "tested" with 60 experiments
(K.D. Shimuzu, M.L.Snapper, and A.H. Hoveyda, *Chemistry,* **1998,** p1885)

"Index Library" Strategy



100 possibilities "tested" with 20 experiments
(C.A. Kreuger, M.L.Snapper, and A.H. Hoveyda, *ACS National Meeting, Boston, Aug 1998*)